UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/594,641	03/28/2008	Yousef Al-Abed	50425/262	1663

1912 7590 10/11/2011

AMSTER, ROTHSTEIN & EBENSTEIN LLP
90 PARK AVENUE
NEW YORK, NY 10016

EXAMINER	
EWOLDT, GERALD R	
ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
10/11/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/594,641	AL-ABED, YOUSEF	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 August 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1,3,11 and 27-37* is/are pending in the application.

5a) Of the above claim(s) *34-37* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1,3,11 and 27-33* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/12/11*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment, remarks, and IDS filed 8/12/11 have been entered.

2. Claims 1, 3, 11, 27, 28-33, and newly added Claims 34-37 are pending.

Claims drawn to a method employing Fab and $F(ab)_2$ fragments were withdrawn in the Office action of 10/15/09. Accordingly, newly added Claims 34-37 are withdrawn from further consideration as being drawn to non-elected species.

Claims 1, 3, 11, and 27-33 are under examination.

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1, 3, 11, 27, and 28 stand rejected under 35 U.S.C. 102(b) as being anticipated by WO 01/64749 (IDS).

As set forth previously, WO 01/64749 teaches the treatment of diabetes (diabetic retinopathy) comprising administering to a human an antibody that inhibits MIF (see particularly page 32 and Claim 53). Said antibodies include monoclonal and humanized antibodies (see particularly pages 9 and 10).

The reference clearly anticipates the claimed invention.

Applicant's arguments, filed 8/12/11, have been fully considered but are not found persuasive. Applicant argues that the reference does not teach a method of inhibiting the progression of type 1 diabetes and that diabetic retinopathy is not type 1 diabetes.

First note that Claims 29-33 are not included in this rejection as is at least implied in Applicant's arguments. Regardless, diabetic retinopathy most certainly is an aspect of type 1 diabetes and its treatment is encompassed by the claims. Also note that it is a progressive disease that results in blindness over time, i.e., a "progression" of type 1 diabetes.

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1, 3, 11, 27, and 29-32 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Bojunga et al. (2003, IDS) in view of Nishihira and Ogata (2001).

As set forth previously, Bojunga et al. teaches the treatment of diabetes comprising the administration of a MIF inhibitor (see particularly page 185). Figure 3 of the reference further teaches that increased MIF-RNA expression precedes that onset of disease. Figure 4 of the reference teaches that from the time of MIF administration 4-10 weeks is required before the onset of disease.

The reference teaching differs from the claimed invention in that it does not teach an antibody MIF inhibitor nor the treatment of human diabetes.

Nishihira and Ogata teach the treatment of autoimmune diseases with an anti-MIF antibody and a small organic molecule and that the treatments are essentially are interchangeable (see particularly **Perspectives**). The reference further teaches that MIF is essential for T cell activation (see particularly page 778, column 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to treat diabetes, as taught by Bojunga et al., with an anti-MIF antibody because Nishihira and Ogata teach that small organic molecules are interchangeable with antibodies in the context of the treatment of autoimmune disease. The choice of either for the treatment of diabetes would not render the method patentably distinct. Regarding the treatment of humans, given that humans are the major suffers of diabetes, the treatment of humans would be obvious. Additionally, it would be obvious to treat a patient at risk of developing disease given the teachings of Bojunga et al. that, a) increased MIF-RNA expression precedes that onset of disease, and b) MIF administration precedes the onset of disease in the experiments of the reference, and c) Nishihira and Ogata teach that MIF is essential for T cell activation. Clearly T cell activation precedes disease onset (given that T cells are disease effectors) thus, it would be obvious to block the disease-causing effects of MIF as well as T cell activation before the onset of disease.

Applicant's arguments, filed 8/12/11, have been fully considered but are not found persuasive. Applicant begins by selectively characterizing the teachings of Bojunga et al. concluding that the reference does not anticipate the claimed invention.

Applicant's position is noted. As set forth above, the rejection is one of obviousness and not anticipation.

Citing newly submitted Greenbaum et al., Applicant argues that elevated mRNA levels do not necessarily predict elevated protein levels. Applicant further argues that Bojunga et al. teaches decreased MIF protein levels in lymphocytes of CY-treated NOD mice.

Regarding the decreased MIF protein levels in the lymphocytes of CY-treated NOD mice taught by Bojunga et al., the reference teaches that intracellular protein in lymphocytes was decreased because it was likely secreted. This finding fits well with the teachings of Greenbaum et al. wherein the measurement of serum levels of secreted proteins correlated 100% of the time with disease in one set of experiments (page 1172, column 2). Further regarding Greenbaum et al., the reference teaches little else about mRNA levels and protein levels of secreted proteins.

Applicant cites newly submitted Ogata et al.

It is unclear why Applicant would submit this reference as it teaches nothing about the method of the instant claims. The reference confirms that MIF was known as a proinflammatory cytokine but was also known to be ubiquitously expressed in a number of tissues. Proteins with different activities in different tissues are known in the art, e.g., BDCA-4/neuropilin-1). That MIF mRNA expression did not correlate with MIF protein expression in a single cell type (expression did correlate in another cell type) can be easily explained by either secretion or degradation of the protein depending on the specific cell or tissue physiology. The reference further teaches that "MIF possesses a unique biological [in the brain] function *beyond the immune system…*" (emphasis by the examiner), further confirming MIF's well-known proinflammatory role. That MIF has an additional function is irrelevant to the claimed invention.

Switching back to Bojunga et al., Applicant argues that the administration of MIF to experimental animals did not cause a statistically significant increase in disease incidence.

The reference teaches that said administration did cause a noticeable increase in disease which is noteworthy as a first experiment with a single dosage (25 µg) of protein.

Applicant argues that Nishihira and Ogata does not anticipate the claimed invention.

Applicant's position is noted. As set forth above, the rejection is one of obviousness and not anticipation.

7. Claims 28 and 33 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Bojunga et al. (2003, IDS) in view of Nishihira and Ogata (2001), as applied to Claims 1, 3, 11, 27, and newly added Claims 29-32 above, in further view of U.S. Patent No. 5,530,101.

As set forth previously, Bojunga et al. and Nishihira and Ogata have been discussed above.

The method of the combined references differs from the claimed method only in that it does not employ a humanized monoclonal antibody. The '101 patent, however, teaches that humanized antibodies are preferred for the treatment of humans because they are less immunogenic to humans (see particularly the Abstract). Thus, the use of a humanized anti-MIF antibody would be preferred and obvious for the treatment of human diabetes.

Applicant has not argued this rejection separately; Applicant reiterates the argument traversing the rejection of the claims in view of Bojunga et al. and Nishihira and Ogata.

See the Examiner's response in section 6, above.

8. Claims 1, 3, 11, 27, and 29-32 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 01/32606 (IDS) in view of Nishihira and Ogata (2001).

As set forth previously, WO 01/32606 teaches the treatment or prevention of type 1 (insulin dependent) diabetes comprising the administration of a MIF inhibitor (see particularly Claim 12).

The reference teaching differs from the claimed invention in that it does not teach an antibody MIF inhibitor nor the treatment of human diabetes.

Nishihira and Ogata teach the treatment of autoimmune diseases with an anti-MIF antibody and a small organic molecule and that the treatments are essentially are interchangeable (see particularly **Perspectives**). The reference further teaches that MIF is essential for T cell activation (see particularly page 778, column 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to treat or prevent diabetes, as taught by WO 01/32606, with an anti-MIF antibody because Nishihira and Ogata teach that small organic molecules are interchangeable with antibodies in the context of the treatment of autoimmune disease. The choice of either for the treatment of

diabetes would not render the method patentably distinct. Regarding the treatment of humans, given that humans are the major suffers of diabetes, the treatment of humans would be obvious. Note that "prevention" encompasses the treatment of an at risk individual.

Applicant's arguments, filed 8/12/11, have been fully considered but are not found persuasive. Applicant argues that WO 01/32606 teaches away from the use of antibodies for the treatment of disease.

A review of the reference discloses the single sentence in the Background (page 2), "Such biological agents [including antibodies], unfortunately, have certain limitations with regard to their clinical utility". Said single sentence hardly comprises a persuasive teaching of any sort.

9. Claims 28 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 01/32606 (IDS) in view of Nishihira and Ogata (2001), as applied to Claims 1, 3, 11, 27, and newly added Claims 29-32 above, in further view of U.S. Patent No. 5,530,101.

As set forth previously, WO 01/32606 and Nishihira and Ogata have been discussed above.

The method of the combined references differs from the claimed method only in that it does not employ a humanized monoclonal antibody. The '101 patent, however, teaches that humanized antibodies are preferred for the treatment of humans because they are less immunogenic to humans (see particularly the Abstract). Thus, the use of a humanized anti-MIF antibody would be preferred and obvious for the treatment of human diabetes.

Applicant has not argued this rejection separately; Applicant reiterates previous arguments.

See the Examiner's response in sections 6-8, above.

10. No claim is allowed.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened

statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ram Shukla can be reached on (571) 272-0841.

13. **Please Note:** Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). Additionally, the Technology Center receptionist can be reached at (571) 272-1600.

/G.R. Ewoldt/
G.R. Ewoldt, Ph.D.
Primary Examiner
Technology Center 1600